# FACTORS ASSOCIATED WITH SICKLE CELL DISEASE SEVERITY AMONG PATIENTS WITH SICKLE CELL DISEASE AT WEBUYE COUNTY HOSPITAL, KENYA.

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**REG NO: SM/PGFM/03/12**

**A THESIS SUBMITTED IN PARTIAL FULFILMENT FOR THE REQUIREMENT OF THE AWARD OF MASTER OF MEDICINE IN FAMILY MEDICINE, MOI UNIVERSITY.**

**2016**

## DECLARATION

"I hereby declare that this thesis is my original work and has not been presented for a degree in any other university/institution."

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Signature …… Date …. /…./……..

**Declaration by the Supervisors:**

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## DEDICATION

I would like to dedicate this work to my wife Florence, my children Bella and Earl.

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## LIST OF ABBREVIATIONS

ACS- Acute Chest Syndrome

AMPATH-Academic Model Providing Access to Healthcare

CCF- Congestive Cardiac Failure

CVA -Cerebrovascular Accident

Hb-Haemoglobin

HbA -Adult Haemoglobin

HbF-Foetal Haemoglobin

IEF- Isoelectric Focusing

IQR-Interquartile Range

IREC -Institutional Research and Ethics Committee

NHIF-National Hospital Insurance Fund

PCR- Polymerase Chain Reaction

POPC-Paediatric Outpatient Clinic

REACH- Realizing Effectiveness of Hydroxyurea across Continents

SCA-Sickle Cell Anaemia

SCC-Sickle Cell Clinic

SCD-Sickle Cell Disease

VOC-Vaso-Occlusive Crisis

WBC-White Blood Cell

WCH-Webuye County Hospital

WHO-World Health Organization

## DEFINITION OF TERMS

**Adverse Outcomes**: death, stroke, frequent pain and recurrent acute chest syndrome.(Quinn, Lee et al. 2008).

**Acute Sequestration Crisis:** rapid onset of trapping of red blood cells in the spleen characterised clinically by a sudden increase in splenic size, at least 2cm below the left costal margin and accompanied by a reduction in haemoglobin or haematocrit by 20% of baseline level.(Makani, Cox et al. 2011)

**Acute Chest Syndrome:** Pulmonary complication of sickle cell disease characterised by fever, chest pain and appearance of new infiltrates on chest radiograph. (Siddiqui and Ahmed 2003)

## ABSTRACT

**Background**: Globally, sickle cell disease (SCD) has its highest prevalence and worst prognosis in sub-Saharan Africa despite the improvements that have been made worldwide in its management and prognosis over the last two decades. An estimated 300,000 children are born with SCD worldwide and three-quarters of these births are in sub-Saharan Africa. There is a high prevalence of sickle cell disease in western Kenya. While some of the patients remain relatively stable, others experience more adverse outcomes and require frequent hospitalizations.

**Objective:** To determine the factors associated with disease severity among patients with Sickle Cell Disease seen in Webuye County Hospital.

**Methods**: This was a descriptive cross-sectional study conducted at Webuye County Hospital inpatient and outpatient departments. The study population consisted of all patients with SCD on follow up and those admitted into the wards during the study period. Using the Fisher's formula, the minimum sample size was calculated to be 108 but a total of 151 were recruited during the study period. The patients were recruited using consecutive sampling method as they came into the clinic and upon admission into the wards. A pre-structured questionnaire was used to collect socio-demographic and anthropometric data. Blood samples were collected for electrophoresis and haemogram analysis. Disease severity was assessed using sickle cell disease severity index. Data analysis was done using software for data and computing known as R (R Core Team 2015). Association between socio-demographic, healthcare utilization and laboratory characteristics with disease severity was assessed. $P<0.05$ was considered significant.

**Results:** Results from 151 participant results were analyzed. The median age of participants was 5 years with a minimum and maximum of 1 and 18 years respectively. Males were more represented at 55.6%. The median age at diagnosis was 1.5 years. Eighty-six participants had mild disease; Fifty-nine had moderate severity while only six had severe disease. There was no association between the socio-demographic characteristics and disease severity. Patients who attended at least three-quarters of their scheduled clinic visits had a significantly mild course of sickle cell disease.

**Conclusions:** There was no association between socio-demographic, laboratory characteristics and disease severity among our patients. Patients who attend at least three-quarters of scheduled follow-up have a mild course of SCD.

**Recommendations:** All patients with SCD in our set up should be sensitized to adhere to prescribed supportive measures with or without SCD crises.

# CHAPTER ONE: INTRODUCTION

## 1.1 Background

Sickle cell anaemia (SCA), the most common inheritable disease in Africa, is a leading public health problem in the region and elsewhere where descendants of Africans have settled. It has been recognized worldwide as a major cause of morbidity and mortality with tremendous social and economic impact.(Mpalampa, Ndugwa et al. 2012). In addition to homozygous state SS, there are at least five other major genotypes linked to the disease. (George and Opara 2011). Available data indicate that sickle cell disease (SS) is the dominant and may be the only form of sickle cell disease in East Africa. (Mpalampa, Ndugwa et al. 2012).This study also reports upto20% frequency of sickle cell trait (AS).

In the Jamaican Cohort Study of Sickle Cell Disease initiated in 1973, the causes of early mortality were described as the major complications such as acute splenic sequestration, pneumococcal septicaemia, aplastic crisis, hypersplenism and acute chest syndrome.(Serjeant and Serjeant 1993). In the Cooperative Study of Sickle Cell Disease carried out from October 1978 through October 1988 in predicting adverse outcomes in children with sickle cell disease, clinical events included stroke, a painful event of the arms, legs, back, abdomen, chest or head that lasted more than two hours and required medical care, dactylitis, acute splenic sequestration, acute chest syndrome, the right upper quadrant syndrome, osteomyelitis and appendicitis.(Kirchner, 2000). In this study the four specific adverse events that

served as proxies for severe sickle cell disease were (1) death related to sickle cell disease (2) stroke (3) an average of at least two painful events per year for three consecutive years and (4) the occurrence of at least one episode of acute chest syndrome yearly. Out of these 392 children, 17.9% had one or more of the four adverse outcomes that qualified their diseases as severe. The mean age at which children were classified as having severe disease on the basis of acute chest syndrome was 3.5 years. The authors concluded that early dactylitis, a steady state Hb level less than 7 g per dl and leukocytosis in the absence of infection predict possibility of severe disease later in life.

Foucan et al in the study of The Paediatric Cohort of Guadeloupe (1984-99) also concluded that dactylitis occurring before six months of life identifies children risk of severe complication who should benefit from close management.(Foucan, Ekouevi et al. 2006).

A study conducted in Nigeria described vasoocclusive crises as the commonest complications of SCD. Other associated morbidities in this study included malaria 34.3%, dactylitis 25.4%, pneumonia 10.7% and osteomyelitis 7.1% .(George and Opara 2011).

A retrospective review of case notes of children with sickle cell anaemia(SCA) seen in the haematology clinic University of Port Harcourt Teaching Hospital, Nigeria in 2009 showed that up to 91.1% of the patients were less than 10 years in age.

This suggests that many patients with sickle cell anaemia in Sub-Saharan Africa die in early childhood compared with the more developed countries where these patients live well into their 40's (George and Opara 2011).

The study done in Kano Nigeria showed the highest prevalence in the 0-5 year age group and lowest in the 21-25 years age group. There was no case found in the age group above 26 years. Sickle cell anaemia contributes the equivalent of 25% of deaths in children under five years old in Africa.(George and Opara 2011).

Although the clinical course of sickle cell disease does not follow a pre-specified, uniform pattern, symptoms of chronic pain, acute anaemia, infection and other potentially debilitating complications are characteristic of the disease. (George and Opara 2011).The Saudi-Indian and Senegal haplotypes of SCD are associated with high HbF levels and carriers of these haplotypes can have a milder course of the disease. Similar findings were also reported in a study conducted at the Sickle Cell Clinic (SCC) of Mulago Hospital in Kampala Uganda.(Mpalampa, Ndugwa et al. 2012).

The World Health Organization (WHO) 2010 statement recognizes that current national policies and plans for SCD are inadequate; appropriate facilities and trained personnel are scarce; diagnostic tools and treatment are insufficient despite SCD being the most prevalent genetic disease in Africa. The statement recommends a comprehensive healthcare management agenda, committed leadership, and effective actions at all levels (World Health Organisation 2010).

## 1.2 Statement of the Problem

Sickle cell disease is common throughout much of sub-Saharan Africa affecting up to 3% of births in some parts of the continent.(Ndila, Bauni et al. 2014). It is estimated that 240,000 children are born with SCD in sub-Saharan Africa. ( Makani et al 2011) Scott D. Grosse et al concluded that although current data are inadequate to support definitive statements, they are consistent with an early mortality of 50% to 90% among children born in Africa with SS disease.(Grosse, Odame et al. 2011).

Sickle cell anaemia contributes the equivalent of 25% of deaths in children under five years in Africa, with up to 16% of such deaths occurring in some West African countries.(George and Opara 2011). Ndeezi et al reported a prevalence of 13.3% for sickle cell trait in Uganda in 2016.(Ndeezi et al 2016)

In a national survey in all hospitals in Kenya between November 1987 to May 1990 carried out by Aluoch J R and Aluoch L H, 77% of patients with sickle cell anaemia were below 15 years of age. This study further found out that 80% of the patients with sickle cell anemia were of Luo or Luhya ethnic origin of western Kenya. (Aluoch and Aluoch 1993). Suchuev et al in a study of the burden and consequences of inherited blood disorders among young children in western Kenya reported the prevalence of HbAS and HbSS to be 17.6% and 1.6% respectively. A similar prevalence was reported by Foote EM et al among children in Nyando District of Nyanza.(Foote, Sullivan et al. 2013). These findings draw attention to the extent of sickle cell disease as a public health problem in Africa and in western Kenya.

This study aims at identifying clinical and laboratory factors that lead to varying severity of sickle cell disease among patients attended to in WCH.

### 1.3 Justification of Study

Globally sickle cell disease (SCD) has its highest prevalence and worst prognosis in sub-Saharan Africa. However relatively few studies describe the characteristics of children with SCD in this region.(Miller, Sleeper et al. 2000).The ability to identify infants with sickle cell anaemia who are likely to have severe complications later in life would permit accurate prognostication and tailoring of therapy to match the disease–related risks.(Sadarangani, Makani et al. 2009). Identifying the characteristics of children with SCD who experience more adverse effects and require more hospitalizations would help stratify these children according to risk categories. A total of 247 children are currently registered on follow up for sickle cell disease at Webuye county Hospital. During the same period 145 patients were admitted into the wards with sickle cell disease and its related complications. Despite the heavy burden of sickle cell disease in Webuye County Hospital, no studies have been done locally to describe the characteristics of these children. Due to the high burden of the disease at Webuye District Hospital such a study is necessary to help stratify these patients and initiate more targeted care. Because of the wide variety in clinical presentation of the disease, this study aims at identifying patients who are likely to develop more complications and prioritize access to the disease modifying care in a setup of limited resources.

### 1.4 Research Question

What are the factors associated with disease severity among patients with sickle cell disease seen at Webuye County Hospital?

### 1.5 Main Objective

To determine the factors associated with disease severity among patients with sickle cell disease seen at Webuye County Hospital.

### 1.6 Specific Objectives

1. To describe the socio-demographic, laboratory characteristics and healthcare utilization among patients with SCD.

2. To describe the relationship between patient characteristics indicated in (1) above and disease severity.

# CHAPTER TWO: LITERATURE REVIEW

## 2.1 Epidemiology

SCD affects 20-25 million people globally, and 50-80% of infants born with SCD in Africa die before the age of five years (Aygun and Odame, 2012).

Ndila C et al reported that SCD is common in many parts of sub-Saharan Africa where it is associated with high early mortality.(Ndila, Bauni et al. 2014). Acording to this study, in the absence of newborn screening most deaths among children with SCD go unrecognized and unreported.

It is estimated that 75-85% of all children born with SCD are born in Africa. (Aygun and Odame, 2012 and Makani et al., 2011)

## 2.3 Morbidity and Mortality

Life expectancy is on the rise for sickle cell patients worldwide but it is still shorter than the general population. The study by Makani J. and Komba A. also indicated that 50% to 80% of the affected children in Africa die annually. However, in some parts of Africa sickle cell disease is still lethal in childhood with only half of the affected children living beyond their fifth birthday. The cause of early mortality in sickle cell disease patients studied in Jamaica were described as acute splenic sequestration,

pneumococcal septicaemia, aplastic crisis, hypersplenism and acute chest syndrome.(Foucan, Ekouevi et al. 2006).

Apart from its somatic manifestations, sickle cell disease impacts individuals and their families both socially and psychologically when trying to meet its demands.

In the past, data on SCD from Africa largely focused on patients in crises and few studies have described the clinical characteristics of patients with SCD at steady–state. (Miller, Sleeper et al 2000). Children who experience hand and foot syndrome in the first year of life tend to experience major sickle cell related complications later in life. Leukocytosis in the absence of infection is associated with major clinical events in children including stroke and is a risk factor for early death in both children and adults with sickle cell disease. (Miller, Sleeper et al 2000). Environmental factors as well as socio economic status may influence the clinical course of sickle cell disease. (Tewari, Brousel et al 2015).

**2.4 Diagnosis**

A study by Okwi et al in Uganda concluded that sickling test would be the best recommended test for screening of SCD as compared to solubility tests in resource-poor settings. This study also recommended Hb electrophoresis as the confirmatory method. Isoelectric focusing (IEF) and high performance liquid chromatography (HPLC) are today still used to screen for haemoglobinopathies in some developed countries. Polymerase chain reaction (PCR) has been useful for both prenatal and

neonatal haemoglobinopathies including SCD in these countries according to the Okwi study.(Okwi, Byarugaba et al. 2010).

**2.5 Severity**

Sickle cell disease is enormously variable in its expression and outcome. It is generally accepted that patients with HbSS and HbSB0 thalasemia have the severe form of sickle cell disease. Patients with HbSC and HbSB+ run a relatively milder course of the disease but are not exempt from its major complications. (Al-Saqladi, Cipolotti et al. 2008).A study conducted by Al-Haggar M et al on the predictors of severity among Egyptian children with SCD concluded that the top three predictors of SCD severity were genotype, basal haemoglobin level and early dactylitis.

(Al-Haggar, Al-Marsafawy et al. 2006). In a study by Miller ST et al, 18% of infants diagnosed with homozygous sickle cell anaemia or sickle cell-Beta0-thalasemia subsequently had an adverse outcome. The adverse outcomes were defined as death, stroke, frequent pain or recurrent acute chest syndrome.(Miller, Sleeper et al. 2000).

The Miller study also concluded that three easily identifiable manifestations of sickle cell disease that may appear in the first two years of life (dactylitis, severe anaemia and leukocytosis) can help to predict the possibility of severe sickle cell disease later in life.

A study carried out by J C Carlos Van-Dunem among hospitalized Angolan children and adolescents, the overall mortality rate from sickle cell disease was 12.9%.Bacterial infections were the most common cause of death (40.1%). Place of

residence out of Luanda (city), lack of outpatient follow up, symptoms onset more than three days, disease manifestation before age of eight months and haemoglobin level <7 g/dl were independent factors related to death. In this study population, sickle cell related deaths were related to quality of health care and access to care. (Can-Dunem, Alves et al.2008).

A study conducted by researchers at the Medical College of Wisconsin, found out that one in three sickle cell disease patients was re-hospitalized within 30 days following the initial hospital visit, a rate 1.5 times greater than that of diabetic patients. This shows that sickle cell patients utilize acute hospital care at a rate higher than the general population. (Wolfson, Schrager et al 2012).

High rates of rehospitalisation within 30 days of a previous hospital stay, an indicator of poor-quality post hospital outpatient care for a number of diseases, has on gained interest related to sickle cell care.(Wolfson, Schrager et al. 2012). This study by Julie A Wolfson et al among sickle cell patients in California identified predictors of higher emergency department utilization to be age greater than 21 years, insurance status, urban location and disease severity. Few previous studies have documented hospital admission rates in Africa for patients with SCD.(Wolfson, Schrager et al. 2012).

A study at Kilifi, Kenya in 2009 described the annual admission rate of 0.45 per patient per year. This study also suggested improved survival of patients with SCD

and found a mortality rate of 1% per year of follow up which compared favourably to that reported in Benin (7%) and Senegal (1.1%). (Sadarangani et al 2009).

A study by Al-Saqladi et al reported poor growth and under-nutrition as common in children with SCD (Al-Saqladi, Cipolotti et al. 2008). This study on the growth and nutritional status of Yemeni children with homozygous SCD concluded that monitoring of growth and nutritional status in children with SCD is an essential requirement for comprehensive care.

## 2.6 Management

Currently there are few documented reliable laboratory tools for the prediction of poor outcomes. These include leukocytosis in the absence of infections, haemoglobin (Hb) levels, HbF%, the globin haplotypes and concurrent thalasaemia. These are derived mainly from large epidemiological studies. (Foucan, Ekouevi et al. 2006). Early diagnosis and simple prophylactic measures significantly reduce deaths associated with homozygous sickle cell disease.

A study by Thomas N. Williams et al published in the Lancet concluded that the introduction of conjugate vaccines against *S. pneumonia* and *H. Influenza* into the childhood immunisation schedules of African countries could substantially improve survival of children with sickle cell anaemia. Most clinical interventions for people with sickle cell disease can be classified as tertiary prevention: for example therapy to

ameliorate anaemia; reduce frequency of pain crises; or prevent stroke recurrence. (Williams et al 2009).

Even though interventions designed in non-malarial areas have significantly improved survival, preliminary data cast doubt on their appropriateness in malarial areas.**(**Ohaeri and Shokunbi 2001) Data on penicillin prophylaxis, for instance, come primarily from developed countries and their relevance in resource-poor settings need to be assessed.(Ebrahim, Khoja et al. 2010). This is due to inadequate microbiologic monitoring and poor survival of these children leading to insufficient data on common infectious threats. Sickle cell anaemia is thus a disease that needs to be thoroughly understood not only by clinicians but also the public in order to reduce its public health effects. (Ebrahim, Khoja et al 2010).

However, considerable lack of knowledge still exists regarding determinants of sickle cell severity. Identification of new risk factors for poor outcome in sickle cell disease is therefore needed for better management of these patients. The disease still remains poorly prioritized in many health programmes. According to Shahul H Ebrahim et al current expenditure on research and care of SCD in resource-poor settings, especially Africa is negligible and sickle disease appears among the most neglected tropical diseases. (Ebrahim, Khoja et al. 2010).

**Tool for Assessing SCD Severity**

Van den Tweel and Van Der Lee developed and validated a severity index for sickle cell disease patients. (van den Tweel, Van Der Lee et al. 2010).

They defined the concept of severity as “the rate and extent of reversible and irreversible damage to organs brought by the SCD process, resulting in the impairment requiring medical interventions.”

This tool assigned more weight to acute life threatening events and neurological complications. A higher score was also assigned to episodes of acute chest syndrome and painful crisis taking into account the frequency of these events.

Another study by Cameron et al developed a different numerical scale. (Cameron, Christian et al. 1983). The first index was based on a numerical score from the clinical history, using six major criteria selected as being reasonably inclusive of clinical manifestations: age at diagnosis, number of hospitalizations, number and types of crises, presence or absence of pneumococcal infection, major organ involvement, and failure to thrive. Points were assigned to each category in rough proportion to the potential for patient mortality or morbidity.

The second index was a sum over the past year of days of hospitalization, number of emergency room visits, and number of units of transfused blood.

Based on these two indices our study adapted the severity index using parameters which are measurable in our setting and assigned proportional weights to each. It was a modification of the Cameron index by an addition of laboratory parameters. Blood transfusions were used as proxy to acute sequestration episodes. The tool was then pilot-tested and adjustments made to it before being used for categorization of our patients according to severity.

**Table 1: Severity Scale for SCD**

| **PARAMETER** | | **SCORE** |
|---|---|---|
| Age at Diagnosis | Less than 12 months<br>12-24 months<br>25 months to 5 years<br>More than 5 years | 3<br>2<br>1<br>0 |
| Number of hospitalizations in past 1 year | 5 or more<br>2-4<br>1 | 3<br>2<br>1 |
| Number of pain episodes(crisis) in past 1 year | 5 or more<br>2-4<br>1 | 3<br>2<br>1 |
| Number of transfusions in the past 1 year | 5 or more<br>2-4s<br>1 | 3<br>2<br>1 |
| Hospitalizations for chest pain, difficulty breathing for more than 2 days requiring oxygen (ACS/severe pneumonia) last year | | 3 |
| Major organ involvement | Stroke<br>CCF | 4<br>4 |
| Musculoskeletal | Necrosis of femoral head<br>Leg ulcers | 3<br>2 |
| Priapism | | 3 |
| Failure to thrive | Less than 3rd percentile Ht/Wt<br>3rd to 10th percentile<br>10th to 25th percentile | 3<br>2<br>1 |
| Laboratory parameters | Hb less than 6.6 gm/dl<br>HbF less than 3%<br>Wbc more than 15,200/cc | 2<br>2<br>2 |
| **MAXIMUM** | | **40** |
| 0-13 =mild<br>14-26 =moderate<br>26+ =severe | | |

# CHAPTER THREE: METHODOLOGY

## 3.1 Study Area/Site

The study was carried out at Webuye County Hospital which is on a 37 acre piece of land in Webuye town, Bungoma East District in Bungoma County along the Eldoret-Bungoma highway, just below the Chetambe Hills. The hospital was built by the African Development Bank under the rural health services fund and started functioning in 1991 being officially opened in 1996.

Webuye County Hospital has an immediate catchment population of 60894 people. It is a high volume level 4 hospital and a referral centre for several other level 4 hospitals surrounding it. The hospital has a bed capacity of 217 beds and bed occupancy of up to 150 percent. On average 150-200 patients are seen on a daily basis. It offers in and Outpatient services. The paediatric ward has a bed capacity of 46 beds catering for both Surgical and medical cases, with an occupancy rate of 111%. The children are seen in Paediatric Triage in the MCH department from where those who require admission proceed to the ward after stabilization in the Emergency room. The Emergency room operates on weekdays between 8am to 5pm.

## 3.2Study Design

Descriptive Cross-sectional study

### 3.3 Study Population

The target population consisted of patients with sickle cell disease attending the outpatient clinic and those admitted to the ward during the study period. A total of 247 patients were targeted according to Webuye District Hospital records (2012).

### 3.4 Sample Size

The sample size was determined using the Fischer's formula as follows;

$$n = Z^2 \times \frac{p(1-p)}{e^2}$$

n=required sample size

Z=confidence level at 95% (standard value of 1.96)

p=estimated prevalence of SCD in projected area -13.3% (Ndeezi et al 2016)

e=margin of error at 5% (0.05)

N= size of target population at WCH 2012 records-247

$n=1.96^2 x 0.133\ (0.867)/0.05^2$

=177

Since the sampling frame is less than 10,000 (247) we adjust the sample size using the formula below

n=n/ (1+n/N)

=177/ (1+177/274)

=108 (minimum sample size)

Where n = Minimum sample size required, N = population size

We recruited up to 151 patients who were all that were attended to during the allocated data collection period.

**3.5 Sampling Procedures**

Consecutive sampling technique was employed in the recruitment of the study subjects.

All patients who consented to the study were recruited as they came into the clinic and on admission to the wards until the sample size was achieved.

### 3.6 Inclusion /Exclusion Criteria

#### 3.6.1 Inclusion

All patients with sickle cell disease seen in the outpatient clinic and those admitted in the ward during the study period were eligible.

#### 3.6.2 Exclusion

All revisits- After the first contact, subjects were not interviewed during their subsequent clinic visits.

### 3.7 Data Collection Instrument

A data collection form was adapted as the main instrument for data collection. It consisted of information on socio-demographic and laboratory characteristics, disease severity, healthcare utilization and medication for SCD. Anthropometric measurements (weight and height) were also collected.

### 3.8 Validity

A pilot study was conducted by the researcher to test the questionnaire for reliability.

The subjects for this phase of the study were selected from WCH clinic and inpatient wards.

The respondents during the pilot study were not recruited into the main study.

### 3.9 Data Collection Procedures

The principal investigator collected the data through hospital record reviews to determine the frequency of admissions, blood transfusions and clinic visits for the participants. Interviewer administered–pretested data collection form was used to collect information on socio-demographic characteristics, disease severity, Healthcare utilization and medication for SCD). In addition, information on anthropometric measurements (weight and height) was also collected. Blood samples were collected for Hb electrophoresis and haemogram analysis.

Five millilitres of whole blood sample was collected for analysis. This was done by trained research assistants, who were clinicians, and the primary researcher. Hb electrophoresis was done at the AMPATH laboratory while complete blood count was done at the WCH laboratory. After analysis, the blood was discarded according to the laid down standards of safety.

### 3.10 Data Management

The completed questionnaires were cleaned and data coded before entering into the Epidata data base in the computer.

**Statistical Data Analysis**

From Epidata the data was exported to software for statistical computing and data analysis (R Core Team, 2015) for analysis. Categorical variables were summarized as frequencies and the corresponding percentages.

Continuous variables were summarized as median and the corresponding inter quartile range (IQR). Gaussian assumptions were assessed using Shapiro Wilks test for normality.

Since the variables violated Gaussian assumptions they were summarized as median and the corresponding IQR. Association between continuous variables was assessed using Spearman rank correlation coefficient. Association between categorical and continuous variables was assessed using two Wilcoxon rank sum test (Mann Whitney U test). Bivariate analysis was used to establish the association between severity of the disease and the potential factors. The variables that were associated with the outcome were incorporated in the multiple linear regression models. The coefficients of the model alongside the corresponding 95% confidence limits (95% CL) were reported. There were variables that were not statistically significant in the bivariate analysis but were however included in the multiple regression model. These variables include the demographic characteristics: age and gender. This is due to the fact that there is a possibility that these variables confound the association between the

outcome and other variables. Another variable was height to weight percentile. It was included because it was statistically identified as a potential confounder.

### 3.11 Ethical Considerations

Approval to conduct the study was sought from the Institutional Research and Ethics committee (IREC) Moi University. Authority from the Webuye District Hospital Management Team was also sought.

Signed informed consent from the parent/guardian of the children was obtained after a clear explanation of the purpose of the study.

Confidentiality of the participants was maintained. The completed data collection forms were kept under key and lock cabinet accessible only to the researcher.

Computerized data was protected by use of password. A verbal assent was obtained from children aged 7 years or more in addition to the consent from the parents or guardians before inclusion into the study.

### 3.12 Study Limitation

The tool for assessing SCD severity was a modification of the original tool developed and validated by Cameron et al in 1983. The findings of our study may not be similar to those obtained by the original tool. This presents significant challenge in comparing our findings to those of studies done using tools not similar to the one used in this study.

## CHAPTER FOUR: RESULTS

A total of 151 participants were analyzed. The median (IQR) age of the participants was 5.0 (IQR: 3.0, 8.0) years with a minimum and a maximum of 1.0 and 18.0 years respectively (Figure 1). Majority of the participants were aged between 2.5 and 7.5 years.

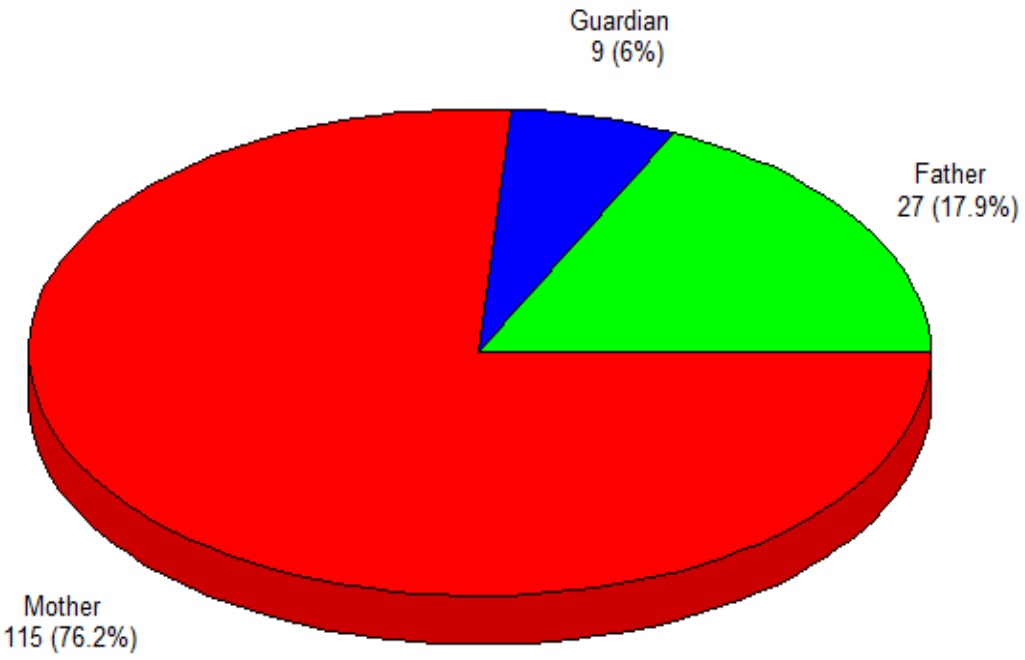


**Figure 1: Caretaker Distribution**

Majority of the participants were under the care of their mothers.

**Table 2: Relationship between the Participants with their Caretakers and the Level of Education of the Caretakers**

| **Caretaker's Level of Education** | **Caretaker** | | | |
|---|---|---|---|---|
| | Father (n=27) | Mother(n=115) | Guardian(n=9) | Total |
| None | 0 (0.0%) | 5 (4.3%) | 0 (0.0%) | 5 (3.3%) |
| Primary | 11 (40.7%) | 57 (49.6%) | 5 (55.6%) | 73 (48.3%) |
| Secondary | 10 (37.0%) | 44 (38.3%) | 3 (33.3%) | 57 (37.7%) |
| Tertiary | 6 (22.2%) | 9 (7.8%) | 1 (11.1%) | 16 (10.6%) |
| Total | 27 (17.9%) | 115 (76.2%) | 9 (6.0%) | 151 (100%) |

48.3% of the caretakers had at least primary level of education while only 3.3% had no formal education.

**Table 3: Access to Health Facility and the Means of Transport**

| **Characteristic** | | **n (%)** |
|---|---|---|
| Travel time | 0-30 Min | 26 (17.2%) |
| | 30-60 Min | 101 (66.9%) |
| | >60 Min | 24 (15.9%) |
| Transport means | On foot | 9 (6.0%) |
| | Motorcycle | 80 (53.0%) |
| | Vehicle | 62 41.1%) |

Majority (66.9%) of the participants had to travel for between 30 to 60 minutes to get to the health facility and the most common means of transport was the motorcycle.

**Table 4: Health-Care Utilization, Physical and Laboratory Characteristics of Participants**

| **Variable** | **n (%) or Median (IQR)** |
|---|---|
| Clinic attendance in the past one year | |
| Not on follow up | 7 (4.6%) |
| <25% | 2 (1.3%) |
| 25-50% | 7 (4.6%) |
| >50% | 135 (89.4%) |
| • 50-75% | 30 |
| • >75% | 105 |
| Having NHIF | 22 (14.6%) |
| Weight | 16.0 (14.0, 22.0) |
| Height | 106.0 (93.0, 121.5) |
| Height/Weight percentile | 6.4 (5.5, 6.9) |
| HBF% | 14.1 (0.0, 20.8) |
| WBC (x 103/cc) | 13.1 (8.9, 20.1) |
| Hb (g/dL) | 7.6 (6.6, 8.8) |
| VOCs | 2.0 (1.0, 3.0) |
| ACS | 0.0 (0.0, 1.0) |

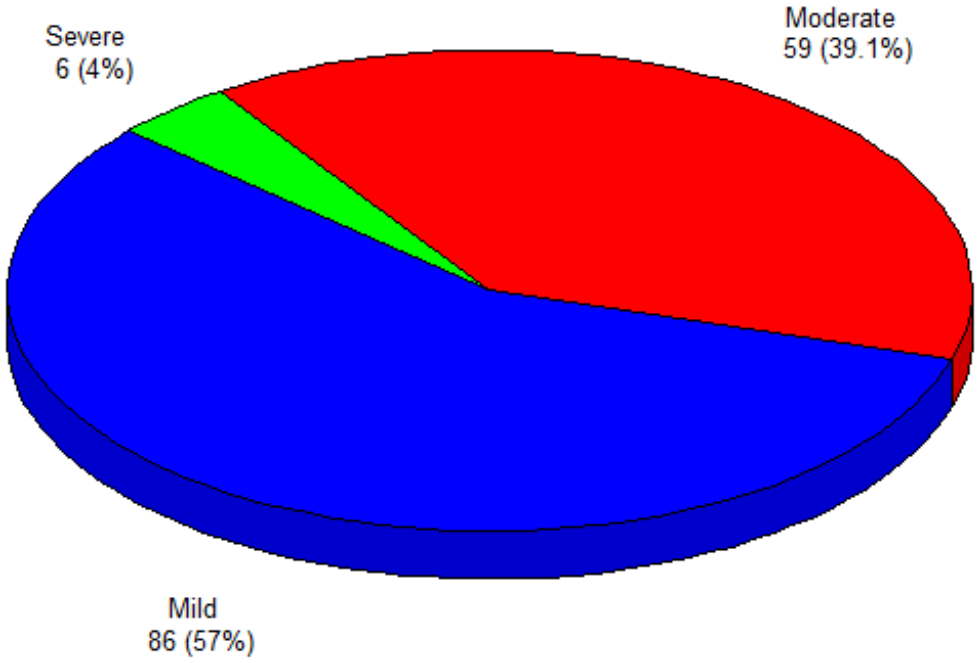


**Figure 2: Degree of SCD severity**

Distribution of disease severity score (0-12=mild, 13-26=moderate, >26=severe)

Majority of the participants (57%) had mild disease while only 4% had severe disease.

**Table 5: Relationship between Participants' Socio-Demographic Characteristics and Disease Severity**

| **Variable** | | **Severity ($r_{spearman}$ / median (IQR))** | **p-value** |
|---|---|---|---|
| Age | | -0.03 | 0.746 |
| Gender | Male | 12.0 (10.0,14.0) | 0.194 |
| | Female | 11.0 (8.5,14.5) | |
| Caregiver | Mother | 11.0 (9.0,15.0) | |
| | Father | 12.0 (9.0,13.5) | 0.968 |
| | Guardian | 11.0 (10.0,13.0) | |
| Caregiver Education level | None<br>Primary<br>Secondary<br>Tertiary | 11.0 (7.0,12.0)<br>11.0 (9.0,14.0)<br>11.0 (9.0,14.0)<br>12.0 (8.8,16.0) | 0.732 |

There was no association between the socio-demographic characteristics and disease severity.

**Table 6: Relationship between Participants' Laboratory Characteristics and Disease Severity**

| **Variable** | **Severity($r$ spearman)** | **p-value** |
|---|---|---|
| HbA% | 0.08 | 0.315 |
| $HbA_2$/C% | 0.04 | 0.663 |
| HbS% | 0.10 | 0.246 |

**Table 7: Relationship between Participants Access to Healthcare and Disease Severity**

| **Variable** | | **Severity ($r$spearman/ median (IQR))** | **p-value** |
|---|---|---|---|
| Travel time to the clinic | <30 minutes | 11.0 (10.0,13.0) | |
| | 30-60 minutes | 11.0 (9.0,15.0) | 0.994 |
| | >60 minutes | 11.5 (9.0,14.0) | |
| Insurance (NHIF) | No<br>Yes | 11.0 (9.0,14.0)<br>12.5 (10.0,13.8) | 0.536 |
| Transport means | Foot | 14.0 (13.0,15.0) | |
| | Motorcycle | 11.0 (9.0,14.0) | 0.267 |
| | Vehicle | 11.0 (9.0,14.0) | |
| Clinic Attendance | >75%<br><75% | 10.0 (8.0,13.0)<br>13.0 (10.0,15.0) | **0.002** |

Patients who attended more than 75% of their scheduled clinic visits had a mild course of SCD.

On further analysis, the scores were reclassified into two groups: “mild” and “moderate/severe”. The association with disease severity was assessed and presented in table 8.

Association between categorical variables was assessed using Pearson’s Chi Square test. Fisher’s exact test was conducted whenever the Chi Square assumptions were violated. Comparison of the continuous variables was done using two-sample Wilcoxon rank-sum test (Mann-Whitney U test). Results were presented using a table.

**Table 8: Factors associated with Disease Severity**

| **Variables** | | **Mild (n = 90)** | **Moderate/Severe (n = 61)** | **p-value** |
|---|---|---|---|---|
| | | **Median (IQR) or n (%)** | **Median (IQR) or n (%)** | |
| Age (Years) | | 5.0 (3.0, 8.0) | 5.0 (3.0, 8.0) | 0.693[w] |
| Sex (Male vs. Female) | | 48 (53.3%) | 36 (59.0%) | 0.601[c] |
| HBS% | | 78.1 (69.4, 84.8) | 76.7 (65.8, 88.8) | 0.659[w] |
| Caretaker | Father | 15 (16.7%) | 12 (19.7%) | 0.790[f] |
| | Mother | 70 (77.8%) | 45 (73.8%) | |
| | Guardian | 5 (5.6%) | 4 (6.6%) | |
| Has NHIF Insurance | | 10 (11.1%) | 11 (18.0%) | 0.334[c] |
| Weight (Kgs) | | 15.5 (14.0, 20.0) | 17.0 (14.0, 22.0) | 0.513[w] |
| Height (cm) | | 105.5 (91.0, 118.8) | 107.0 (94.0, 122.0) | 0.400[w] |
| BMI ($Kgs/m^2$ ) | | 15.0 (13.9, 16.4) | 15.3 (13.9, 17.0) | 0.650[w] |
| HBA% | | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.914[w] |
| HBA2/C% | | 2.9 (2.5, 3.3) | 2.8 (2.5, 3.2) | 0.678[w] |

P – Is the p-value; [c] Chi Square test; [f] Fisher's exact test; [w] two-sample Wilcoxon rank-sum test

None of the variables assessed was associated with the outcome (severity of the disease), p values >0.05.

## CHAPTER FIVE: DISCUSSION

From our study findings the mean age of the participants was five years. Fifty- seven percent were aged between two and a half years and seven and a half years. Only one participant was 18 years old. This finding was similar to that of George and Opara in 2011. They reported that 91.1% of their participants were 10 years of age and below pre supposing that many of our patients are dying in early childhood. (George and Opara 2011).`This is in contrast to the significant improvements in morbidity and mortality rates for children with SCD in high resource countries due to factors such as early diagnosis thorough newborn screening, prophylactic therapy and comprehensive care including hydroxyurea therapy.(Mulumba and Wilson 2015).

There was no difference in age distribution between the males and the females in our study even though males were slightly more represented at 55.6%. We can conclude that males and females were affected in equal proportion. Kondani et al reported a similar sex ratio of 1:1 in a Congolese study (Kondani, Gini-Ehungu et al. 2014).

The mean age at diagnosis was 18 months. The maximum age at diagnosis was 10 years. In comparison to the findings by Adoku et al from Nigeria in 2013, this was slightly lower. In their study, the mean age at confirmation of haemoglobin genotype was at 27.33 months (Akodu, Diaku-Akinwumi et al. 2013).

They also concluded that too few subjects were diagnosed at infancy. Routine screening should ideally be done at birth and neonatal period. McGann et al in a prospective newborn screening and treatment program for SCA in Luanda, Angola

stated that early identification by newborn screening followed by simple interventions dramatically reduced mortality of SCA in the United States but this strategy is not yet established in Africa.(McGann, Ferris et al. 2013).

They concluded that newborn screening and treatment for SCA appear to be highly cost-effective across all scenarios for Angola by WHO criteria.

The similarity between our findings and these studies can be explained by the fact that they were studies carried out in developing countries with similar healthcare challenges.

In our study, patients who attended at least seventy-five percent of their scheduled clinic visits had a significantly milder clinical course of SCD compared to those who did not. Used as a proxy measure for comprehensive care, adherence to clinic follow-up supports comprehensive care in modifying the course of SCD. Ansong et al in their study concluded that emphasis should be placed on early counselling, newborn screening, antimicrobial prophylaxis, vaccination against infections, as well as training of healthcare workers, patients and caregivers (Ansong, Akoto et al. 2013). Their study also reported that these interventions were affordable in developing countries.

None of our patients were on hydroxyurea but majority were on folic acid, malaria prophylaxis and penicillin.

Saidi et al on their experience in North-western Tanzania reported prescription for folic acid at 92.7% and malaria prophylaxis at 84.7% (Saidi, Smart et al. 2015). None of their subjects were on hydroxyurea.

They concluded that opportunities still exist to improve care through wider access to screening and diagnosis as well as better coordination of care.

Amendah et al in their study of a rural facility in Kilifi District, Kenya described the first published estimate of the cost of routine outpatient care to range between 94 to 229 US dollars annually(Amendah, Mukamah et al. 2013). Similar conclusions were also reported by Aloni and Nkee from a study in the Democratic Republic of Congo. (Aloni and Nkee 2014).

Julie Makani et al reporting on their experience from Tanzania on interventions to reduce under-five mortality concluded that key policies that governments in Africa are able to implement would reduce mortality in SCD focusing on newborn screening, prevention of infections using penicillin plus prompt diagnosis and treatment of complications(Makani, Soka et al. 2015).

Countries such as the United States and United Kingdom have reduced mortality from SCA from 3 to 0.13 per 100 person years of observation (PYO) with interventions such as newborn screening and comprehensive care(Makani, Ofori-Acquah et al. 2013). Significant improvements in morbidity and mortality among children due to these simple interventions have also been reported by King et al among Jamaican children (King, Knight-Madden et al. 2014). The improvement on

the average life expectancy of people with SCA in the United States has been attributed to newborn screening, penicillin prophylaxis and pneumococcal vaccination.

George et al also reported an average age at diagnosis of 31.2 months (George and Opara,2011) while J.P Ambe et al reported that most children were diagnosed between 6-11 months followed by 1-5 years in a Northern Nigeria study(Ambe, Mava et al. 2013).

There was no association between caregiver characteristics, accessibility to health facility, health insurance status, and disease severity in our study.

This finding was similar to the findings of a study done by Adegoke et al among children with sickle cell disease from South-Western Nigeria.(Adegoke, Adeodu et al. 2015).

They concluded that socio-demographic characteristics have little influence on the development of complications in children with sickle cell disease. However Sanjay et al when studying environmental determinants of severity of sickle cell disease concluded that socio demographic characteristics influence severity of sickle disease (Tewari, Brousse et al. 2015).

They referred to the Cooperative Study of Sickle Cell Disease in the USA. This study found a higher disease burden among children of single parents among African Americans.(Gill, Sleeper et al. 1995). Similarly, Tewari et al concluded that socioeconomic status was undoubtedly associated with sickle cell disease

complications but little had been studied beyond reporting that the disease was associated with a decrease in some measures of social status.(Tewari, Brousse et al. 2015).

The difference in our findings could be explained by the fact that in our study we limited the socioeconomic characteristics to the level of education, insurance status and ease of accessing health facilities. The other studies also incorporated the income of the families.

# CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

## 6.1 CONCLUSION

Patients who attended at least seventy-five percent of the scheduled follow up visits have a significantly mild course of sickle cell disease.

## 6.2 RECOMMENDATIONS

All patients with SCD should be sensitized to adhere to prescribed supportive measures with or without SCD crises.

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## APPENDIX 1: QUESTIONNAIRE

Date……..

Serial Number .....

### I. Socio-Demographic Characteristics

1. Age.....years

**O** less than 12 months

**O** 12 months to 5 years

**O** 6 years to 10 years

**O** more than 10 years

2. Gender

**O** Male

**O** Female

3. Relationship with caregiver

**O** Caregiver is father

**O** Caregiver is mother

**O** Caregiver is sibling

**O** Caregiver is grand parent

**O** Other, specify.....

4. Level of education of caregiver

**O** No formal education

**O** Primary **O** Secondary **O** Tertiary

5. Occupation of caregiver

**O** Formally employed

**O** Cash crop farmer

**O** Casual labourer

**O** Self employed

**O** Unemployed

**II. Disease Severity**

1 .Age at Diagnosis.....years

**O** less than 12 months

**O** 12-24 months

**O** 25 months to 5 years

**O** more than 5 years

2. Number of hospitalizations (admissions) since birth..... (Number)

**O** 5 or more

**O** 2 to 4

**O** 1

3. Number of painful episodes requiring hospitalization since birth..... (Number)

**O** 5 or more

**O** 2 to 4

**O** 1

4. Hospitalizations for chest pain and difficulty in breathing requiring oxygen therapy and lasting more than 2 days.....

**O** 5 or more

**O** 2 to 4 **O** 1

5. Number of blood transfusions received last year..... (Number)

**O** 5 or more

**O** 2 to 4

**O** 1

6. Age when child first experienced painful hands and feet..... (Number)

**O** less than 12 months

**O** 12 -24 months

**O** 25 months to 5 years

**O** more than 5 years

7. Other complications

| | Present | Absent | Don't know |
|---|---|---|---|
| Stroke | | | |
| Priapism | | | |
| Leg ulcer | | | |

**III. Health care utilization**

1. Clinic (POPC) attendance in the past 1 year

**O** Not on follow- up

**O** less than 25% visits attended

**O** 25% to 50% visits attended

**O** more than 50% visits attended

2. Immunization according to KEPI schedule

| | Yes | No | Don't know | Verified from records | Not verified |
|---|---|---|---|---|---|
| Fully immunized (up to date) | | | | | |
| Received Pentavalent vaccine | | | | | |
| Received Pneumovax vaccine | | | | | |

3. Medication for SCD

| | Taking | Not taking | Don't know | Verified from records | Not verified |
|---|---|---|---|---|---|
| Proguanil (palludrine) | | | | | |
| Folic acid | | | | | |
| Benzathine penicillin injection | | | | | |
| Hydroxyurea | | | | | |

4. By what means do you travel to this hospital (clinic) **O** private car

**O** walking

**O** bicycle

**O** motorbike

**O** Matatu

5. How much does it cost to travel to this hospital..... (KShs)

**O** less than KShs. 50

**O** KShs 50 to 100

**O** More than KShs 100

6. How much does it cost to travel to your nearest health facility.....(KShs)

**O** less than KShs 20

**O** KShs 20 to 50

**O** KShs 50 to 100

**O** More than KShs 100

7. Other Siblings diagnosed with SCD.....(number)

**O** Yes

**O** No

8. Other siblings died of SCD.....(number)

**O** Yes

**O** No

9. Caregiver's Health insurance

**O** NHIF

**O** Private Insurance

**O** Not insured

**O** Other, specify

9. Where do you seek help first when the child falls sick?

**O** Neighbour

**O** Church

**O** Traditional healer

**O** Other, specify

## IV. Physical and Laboratory Characteristics

1. Weight.....kg

2. Height.....cm

| | Yes | No |
|---|---|---|
| Fever | | |
| Splenomegaly | | |
| Hepatomegaly | | |
| Displaced apex beat | | |
| Heart murmur | | |
| CCF (diagnosed) | | |
| CVA(diagnosed) | | |

3. Hb.....g/dl

4. White cell count..... x $10^3$/cc

5. Platelet count.....x $10^3$/cc

6. Hb Electrophoresis

**O** SS

**O** AS **O** SC **O** Other specify.....

7. HBF%.....

## APPENDIX 2: CONSENT FORM

Sickle cell disease is an inherited blood disorder that runs in families. It is caused by production of abnormal red blood cells that are easily deformed and clog blood vessels. It is characterised by painful episodes especially of the long bones, and chest, low levels of haemoglobin (the oxygen-carrying molecules in blood) and recurrent infections .It requires long term follow up for successful management of its complications. It is common in western Kenya and a major cause of death in children. Joint effort by caretakers or families and health workers is an important aspect in the management of this disease. The goal of management of sickle cell disease is to control pain, prevent and treat infections, maintain good haemoglobin levels and manage its complications. We are conducting this study to determine the characteristics of children who are at higher risk of complications due to sickle cell disease.

We will use the findings of this study to identify children at higher risk of complications of sickle cell disease and formulate more focused management strategies of these children. These results will also be published in journals for other health workers to read and hopefully influence the care of sickle cell disease in our country and internationally.

The participants will undergo few procedures which will include measurement of height, weight, and examination of body systems by the interviewer. A blood sample will be drawn to test for Haemoglobin analysis and HIV testing.

The procedures will be risk free but will have some discomfort and slight pain.

All findings will be confidential and your participation will not be disclosed to anybody outside the research setting.

The blood test will be done for free and there will be no payments for participation. You will also be required to give consent for the samples to undergo HIV testing.

Your participation in this research is voluntary, and you will not be penalised or suffer any loss if you refuse to participate.

For any question or complains about the research, contact Dr. Owino on the phone number 0702769492 or the administration of Webuye district hospital.

The reasons why this study is being conducted have been explained to me clearly and concisely. All my questions and concerns have been addressed to my satisfaction. I also give consent for HIV testing.

I willingly volunteer to participate in this study and will not expect any monetary gain.

Name: ……

Signature: …….. Date: …

Witness……..

Name: ……

Signature: …….. Date: ….....…